



## Original article

# Comparative study of changes of corneal curvatures and uncorrected distance visual acuity prior to and after corneal collagen crosslinking: 1-year results



Masoud Safarzadeh <sup>a,\*</sup>, Nader Nasiri <sup>b</sup>, Asgar Doostdar <sup>a</sup>, Mohammad Kamali <sup>c</sup>

<sup>a</sup> Department of Optometry, Iran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Department of Ophthalmology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>c</sup> Department of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran

## ARTICLE INFO

## Article history:

Received 8 January 2016

Received in revised form

15 June 2016

Accepted 16 June 2016

Available online 21 August 2016

## Keywords:

corneal curvature

crosslinking

progressive keratoconus

uncorrected distance visual acuity

## ABSTRACT

**Background/Purpose:** Keratoconus is the most common primary corneal ectatic disease and has considerable importance in public health. Corneal collagen crosslinking (CXL) is a procedure to mitigate progression of keratoconus and reduce demand for corneal transplantation. The aim of this study was to evaluate the effect of CXL on corneal topographic and uncorrected distance visual acuity (UDVA) by Oculus Pentacam in the 15–30-year-old population.

**Methods:** In this descriptive–analytic study, we enrolled 38 eyes of 27 patients suffering from progressive keratoconus who were candidates for CXL. UDVA and the anterior and posterior corneal curvatures assessed prior to and 12 months after CXL. Data were analyzed by the paired *t* test and  $p < 0.05$  was considered significant.

**Results:** One year after the CXL, mean UDVA significantly improved  $0.1 \pm 0.25$  logarithm of the minimal angle of resolution ( $p = 0.012$ ). Changes for steep keratometry values, flat keratometry, and mean keratometry on the anterior corneal surface were statistically significant (all  $p < 0.005$ ). However, the difference observed in maximum keratometry and astigmatism was not significant ( $p = 0.421$  and  $p = 0.745$ , respectively). After 12 months, all four keratometry values on the posterior corneal surface had increased significantly ( $p < 0.005$ ), while no significant change observed in astigmatism ( $p = 0.303$ ).

**Conclusion:** Corneal collagen crosslinking has been revealed as an effective and minimally invasive intervention for the treatment of progressive keratoconus that can improve UDVA.

Copyright © 2016, The Ophthalmologic Society of Taiwan. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Keratoconus is a bilateral noninflammatory disease. One of its characteristics is reduction of biomechanical strength of cornea and stromal thinning, which gradually decreases corneal thickness and induces irregular astigmatism, myopia, corneal scarring, and reduction of visual acuity.<sup>1</sup> The incidence and prevalence of keratoconus are 50–230 and 54.4 per 100,000 in the general population, respectively.<sup>2,3</sup> It usually starts at the age of puberty and progresses until the 3<sup>rd</sup>–4<sup>th</sup> decades of life. The most severe stage of the disease occurs at age 20–40 years.<sup>1,4</sup> For early stages of

keratoconus, one would use spectacles and contact lenses though the progression of the disease can lead to irregular astigmatism or corneal scarring, leaving no option other than corneal transplantation in about 20% of patients.<sup>5</sup> Corneal transplantation is an expensive procedure with many complications such as high astigmatism and graft rejection; hence, seeking for a way to halt this progressive disease seems to be of crucial importance.<sup>6–8</sup> For more than a decade, corneal crosslinking (CXL) with riboflavin (vitamin B2) and UV-A has been considered as the only method for improving corneal biomechanical power.<sup>9</sup> UV-A and riboflavin increase the connections of collagen fibers in cornea, which would stabilize the corneal biomechanical indices.<sup>10,11</sup> In this study, we sought to assess the efficacy of riboflavin UV-A light-induced crosslinking in stopping the progression of keratoconus and to compare the anterior and posterior corneal curvatures and uncorrected distance visual acuity (UDVA) prior to and 1 year after

Conflicts of interest: The author declared that they have no competing interests.

\* Corresponding author. Department of Optometry, Iran University of Medical Sciences, Nezam St., Shahnazari St., Madar Sq., Mirdamad Blvd., Tehran, Iran.

E-mail address: [safarzade\\_masoud@yahoo.com](mailto:safarzade_masoud@yahoo.com) (M. Safarzadeh).

<http://dx.doi.org/10.1016/j.tjo.2016.06.003>

2211-5056/Copyright © 2016, The Ophthalmologic Society of Taiwan. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

crosslinking by Pentacam criteria. We also aimed to evaluate whether this procedure can reduce the need for corneal transplantation.

## 2. Methods

In this prospective clinical trial, we enrolled 38 eyes of 27 patients suffering from keratoconus who were candidates for CXL and were eligible for this surgery. The inclusion criteria were: patients with mild to moderate keratoconus; maximum keratometry value (K reading) < 60 diopter (D); minimal corneal thickness > 400  $\mu\text{m}$ ; and age between 15 years and 30 years. This clinical trial was conducted in 2015 and 2016. Patients were randomly selected from those who were referred to an eye hospital and had the diagnosis of progressive keratoconus. Progressive keratoconus was defined as one or more of the following changes over a period of 24 months: an increase of 1.00 D or more in the steepest keratometry ( $K_s$ ) measurement; an increase of 1.00 D or more in manifest cylinder; and an increase of 0.50 D or more in manifest refraction spherical equivalent. Patients with the following criteria were excluded from the study: history of herpetic keratitis; history of previous eye surgery; severe dry eye; corneal infection; history of autoimmune disorders; and usage of hard contact lens for 1 month prior to the study.

The sample size was calculated based on  $Z_\alpha = 1.96$ ,  $Z_\beta = 0.84$ ,  $S_d = 4.4$ , and  $\Delta_\mu = 2$  (D); finally 38 eyes were included in the study. The protocol was described to all the participants and informed consent was obtained. Nonconsenting individuals were excluded from the study. We also described the necessity of this surgery and efficacy of CXL in halting the disease progression to the participants. The study protocol was approved by the ethical committee of Iran University of Medical Sciences (IUMS), Tehran, Iran. All eyes had a complete ophthalmological evaluation, including keratometry, UDVA measurements, slit-lamp biomicroscopy (under low illumination to avoid reflex tearing), and Rotating Scheimpflug topography (Pentacam HR; Oculus Optikgeräte GmbH, Wetzlar, Germany) prior to and 1 year after the CXL. The UDVA was recorded as Snellen value at the initial consultation and 12 months postoperatively and converted to logarithm of the minimal angle of resolution (logMAR) for statistical analyses. Topography measurements were obtained using a rotating Scheimpflug camera (Pentacam, Oculus Optikgeräte GmbH). The Scheimpflug system generates a three-dimensional model of the cornea and anterior segment that can evaluate the severity of keratoconus and to evaluate the progression or regression rates using these indices.<sup>12,13</sup> Topographic data were obtained preoperatively and 12 months postoperatively. Maximum K values ( $K_{\text{max}}$ ), mean K values ( $K_{\text{mean}}$ ), flat K values ( $K_f$ ), and steep K values ( $K_s$ ), as well as corneal astigmatism were recorded from the topography data generated by the Scheimpflug system.

Surgical technique was as follows. After local anesthesia was administered with tetracaine solution 1% (Sina Darou, Tehran, Iran) under sterile condition, the corneal epithelium was removed mechanically. Then, the cornea was impregnated with standard isotonic riboflavin solution 0.1% (Collagex; LightMed, San Clemente, CA, USA) every 5 minutes for 30 minutes, followed by UV-A irradiation at 5 cm for 30 minutes. After 1 hour of surgery, ciprofloxacin 0.3% eye drops (Sina Darou, Tehran, Iran) were used and a bandage lens was placed on the cornea. Then, betamethasone 0.1% (Sina Darou) and ciprofloxacin 0.3% (Sina Darou) were applied four times a day for 1 week. After this, the contact lens was removed and fluorometholone 0.1% eye drops (Sina Darou) were applied three times a day for 3 weeks. All patients' clinical assessments were performed by a single optometrist. One year after CXL, postoperative examinations were carried out in the same way as the

preoperative examinations: slit lamp examination; UDVA; refraction; and corneal topography with Pentacam topographer (Oculus Optikgeräte GmbH).

Statistical analysis was performed using SPSS 19.0 (IBM, Armonk, NY, USA) software. The paired *t* test was used to check the significance of the difference between two dependent groups in every continuous variable. Statistical significance was assessed at 0.05 probability level and  $p < 0.05$  was considered significant. All the values are presented as mean  $\pm$  standard error of the mean or *n* (%).

## 3. Results

This was a prospective interventional study that included 38 eyes of 27 patients. The mean age of patients was 22.5 years (range, 15–30 years) and 55.55% of them were male. At slit-lamp examination performed 12 months after CXL, all the eyes were cleared. There were no serious complications such as infection or corneal scar. The results indicated a significant improvement in UDVA ( $0.10 \pm 0.25$  logMAR;  $p = 0.012$ ). In addition, changes for  $K_s$  ( $0.75 \pm 1.09$ ;  $p < 0.005$ ),  $K_f$  ( $0.79 \pm 1.23$ ;  $p < 0.005$ ), and  $K_{\text{mean}}$  ( $0.79 \pm 1.10$ ;  $p < 0.005$ ) in the anterior corneal surface were significant. The maximum keratometry ( $0.21 \pm 1.65$ ;  $p = 0.421$ ) and anterior surface astigmatism ( $0.04 \pm 0.84$ ;  $p = 0.745$ ) showed no significant changes. One year after CXL, curvatures of the posterior corneal surface significantly increased, but the astigmatism level showed no significant changes ( $0.03 \pm 0.21$ ;  $p = 0.303$ ). Changes in  $K_s$ ,  $K_f$ ,  $K_{\text{mean}}$ , and  $K_{\text{max}}$  of the posterior corneal surface were:  $0.12 \pm 0.18$ D,  $0.14 \pm 0.16$  D,  $0.12 \pm 0.12$  D, and  $0.24 \pm 0.19$  D ( $p < 0.005$ ), respectively. The pre-CXL and 1-year postoperative data in patients with progressive keratoconus, including the Pentacam results and the UDVA are shown in Table 1. Also, results of Scheimpflug topographic measurements in a typical patient are presented in Table 2.

## 4. Discussion

Corneal CXL is a promising new treatment for keratoconus and corneal ectasia.<sup>7,11</sup> It has been repeatedly demonstrated to be successful in stabilizing progressive corneal ectatic disorders with a good safety profile. In CXL, the interaction of UV-A (365 nm) and riboflavin leads to crosslinking within the collagen and intracellular matrix of the stroma, most predominantly in the anterior 300  $\mu\text{m}$ , resulting in strengthening of the cornea.<sup>8,10</sup> In many cases, moreover, CXL improves the patient's visual, refractive, and topographic outcomes with few reported complications.<sup>12,13</sup> Therefore CXL is probably the only true treatment for corneal ectasia that directly addresses the disease pathology and potentially avoids the need for corneal transplantation.

Various studies have been conducted on the effect of this method as an intervention that can be effective in controlling progressive keratoconus; hence this study aimed to investigate its effectiveness by assessing corneal curvature changes and UDVA. Furthermore, the results of this study are showing significant changes in UDVA, steep, flat, and mean of corneal front surface curvatures and suggest that keratoconus did not only progress in the study population but also improved (Table 1). These findings were consistent with several previous studies.<sup>13–15</sup> In addition,  $K_{\text{max}}$  represented stability in keratoconus level. However, the difference in the values may be due to sample size, patients' age, follow-up periods, keratoconus intensity, and the location of cone. Steinberg and colleagues<sup>16</sup> showed changes of the anterior and posterior corneal curvatures 2 years after the CXL for progressive keratoconus. They reported that the mean of the flat and steep curvatures in the anterior corneal surface after 2 years the CXL,

**Table 1**  
Mean distribution and standard deviation (SD) of the variables prior to and 12 months after CXL.

|  | No. of eyes | Preoperative<br>(mean ± SD) | Postoperative<br>(mean ± SD) | Mean difference<br>(mean ± SD) | <i>p</i> |
|--|-------------|-----------------------------|------------------------------|--------------------------------|----------|
| Uncorrected distance visual acuity (logMAR)          | 38          | 0.56 ± 0.51                 | 0.45 ± 0.42                  | 0.10 ± 0.25                    | 0.012    |
| Steep keratometry of anterior corneal surface (D)    | 38          | 47.35 ± 3.22                | 46.60 ± 3.06                 | 0.75 ± 1.09                    | <0.005   |
| Flat keratometry of anterior corneal surface (D)     | 38          | 44.22 ± 2.70                | 43.42 ± 2.82                 | 0.79 ± 1.23                    | <0.005   |
| Mean keratometry of anterior corneal surface (D)     | 38          | 45.73 ± 2.85                | 44.94 ± 2.82                 | 0.79 ± 1.10                    | <0.005   |
| Maximum keratometry of anterior corneal surface (D)  | 38          | 50.58 ± 3.75                | 50.36 ± 4.29                 | 0.21 ± 1.65                    | 0.421    |
| Astigmatism of anterior corneal surface (D)          | 38          | 3.13 ± 1.58                 | 3.18 ± 1.68                  | 0.04 ± 0.84                    | 0.745    |
| Steep keratometry of posterior corneal surface (D)   | 38          | 7.08 ± 0.60                 | 7.21 ± 0.65                  | 0.12 ± 0.18                    | <0.005   |
| Flat keratometry of posterior corneal surface (D)    | 38          | 6.37 ± 0.46                 | 6.51 ± 0.51                  | 0.14 ± 0.16                    | <0.005   |
| Mean keratometry of posterior corneal surface (D)    | 38          | 6.37 ± 0.46                 | 6.51 ± 0.51                  | 0.12 ± 0.12                    | <0.005   |
| Maximum keratometry of posterior corneal surface (D) | 38          | 5.08 ± 0.52                 | 4.84 ± 0.55                  | 0.24 ± 0.19                    | <0.005   |
| Astigmatism of posterior corneal surface (D)         | 38          | 0.72 ± 0.33                 | 0.68 ± 0.40                  | 0.03 ± 0.21                    | 0.303    |

D = diopters; logMAR = logarithm of the minimal angle of resolution; UDVA = uncorrected distance visual acuity.

**Table 2**  
Results of Scheimpflug topography in a typical patient.

| Parameter                                   | Preoperation | 12 months<br>postoperation |
|---|--------------|----------------------------|
| Anterior surface of cornea                  |              |                            |
| Steep keratometry (D)                       | 47.7         | 46.90                      |
| Flat keratometry (D)                        | 44.2         | 43.52                      |
| Mean keratometry (D)                        | 45.95        | 45.2                       |
| Maximum keratometry (D)                     | 50.61        | 50.38                      |
| Astigmatism (D)                             | 3.50         | 3.42                       |
| Posterior surface of cornea                 |              |                            |
| Steep keratometry (D)                       | 7.1          | 7.25                       |
| Flat keratometry (D)                        | 6.4          | 6.6                        |
| Mean keratometry (D)                        | 6.75         | 6.9                        |
| Maximum keratometry (D)                     | 7.3          | 7.4                        |
| Astigmatism (D)                             | 0.7          | 0.65                       |
| Uncorrected distance visual acuity (logMAR) | 0.57         | 0.45                       |

D = diopters; logMAR = logarithm of the minimal angle of resolution.

respectively, 0.8 D and 0.5 D decreased significantly ( $p < 0.005$ ). Our results showed similar facts: the flat and steep curvatures on the anterior corneal surface (0.79 D and 0.75 D, respectively) decreased significantly after the CXL ( $p < 0.005$ ). In our study, sample size was greater and also, the posterior corneal curvatures were evaluated.

A 2013 retrospective study by Toprak and Yildirim<sup>14</sup> on 59 eyes of 47 patients in Turkey illustrated the effect of CXL on  $K_{max}$  and UDVA. They reported that mean UDVA and  $K_{max}$  after CXL improved significantly ( $p < 0.001$ ). In our study, the difference for UDVA was significant ( $p = 0.012$ ), but statistical analysis of the  $K_{max}$ , showed no significant difference between prior to and 1 year after the operation ( $p = 0.421$ ). Thus, although the two studies found an improvement in UDVA after CXL, this insignificant difference for  $K_{max}$  can be attributed to the severity of keratoconus, location of the cone, and age of patients. In Toprak and Yildirim's<sup>14</sup> study, curvatures of the  $K_s$ ,  $K_f$ ,  $K_{mean}$ , and astigmatism value on the anterior or posterior corneal surfaces were not evaluated. Legare et al<sup>15</sup> assessed the safety and efficacy the CXL on 39 eyes of 30 patients and found that the UDVA from preoperative to 2 years postoperative on mean 0.39 logMAR had improved ( $p < 0.001$ ). Although topographic indices remained stable and did not show significant changes. In our study, UDVA from before CXL to 1 year after CXL was improved by mean 0.1 logMAR. Duration of follow-up and how the UDVA was measured prior to and after the operation may explain the difference in the mean UDVA in the two studies.

In a prospective case series study by Hashemi et al<sup>17</sup> on 40 eyes of 32 patients to evaluate CXL long-term results of patients with progressive keratoconus, mean UDVA decreased from  $0.67 \pm 0.52$  logMAR prior to surgery to  $0.65 \pm 0.51$  logMAR 5 years after

surgery. The average of  $K_{max}$  and  $K_{mean}$  were reduced by  $0.16 \pm 2.20$  D and  $0.1 \pm 1.69$  D, respectively. Additionally, astigmatism level changed from  $3.14 \pm 2.22$  D to  $2.49 \pm 1.71$  D. They concluded that  $K_{mean}$ ,  $K_{max}$ , UDVA, and astigmatism did not change during the 5 years after surgery, while CXL is a safe operation that can stop keratoconus progression and limit the need for keratoplasty. Our findings support these findings where the mean UDVA varied from  $0.56 \pm 0.51$  logMAR prior to surgery to  $0.45 \pm 0.42$  logMAR after surgery, while the variations of average  $K_{max}$  and  $K_{mean}$  values occurred within the ranges of  $0.21 \pm 0.65$  D and  $0.79 \pm 0.10$  D, respectively. Change of astigmatism was from  $3.13 \pm 1.58$  D to  $3.18 \pm 1.68$  D. This insignificant difference can be attributed to the study duration, keratoconus severity (bias caused by the inclusion of  $K_{max}$  value), location of cone and patients' age. However, Hashemi et al<sup>17</sup> did not study the steep and flat curvatures of the anterior corneal surface alone, or evaluate the curvatures and astigmatism level of the posterior corneal surface. Hersh et al<sup>18</sup> in New Jersey reported changes in the UDVA and corneal topography 1 year after CXL in patients with progressive keratoconus and corneal ectasia. The study was performed on 71 eyes and the difference in the mean UDVA between prior to and 12 months after the CXL was as follows: the mean UDVA preoperative was  $0.84 \pm 0.34$  logMAR and the mean UDVA postoperative was  $0.77 \pm 0.37$  logMAR ( $p = 0.04$ ) and  $K_{max}$  1 year after the operation was decreased in keratoconus patients;  $2/0 \pm 4/4$  D ( $p = 0.002$ ). In our study, comparison of UDVA and  $K_{max}$  prior to and after CXL showed that the difference for UDVA was statistically significant ( $p = 0.012$ ), whereas that for  $K_{max}$  was not ( $p = 0.421$ ). Evaluation of the posterior corneal surface curvatures was not done by Hersh et al.<sup>18</sup> In the current study, the assessment of posterior surfaces showed that although curvatures significantly increased, the increases are not clinically significant compared to the anterior surface changes. This means that the CXL does not have a positive effect on back surface curvatures, while the trivial impact of corneal posterior compared to the anterior surface on eye refraction can be the reason for not addressing the assessment of posterior surfaces in other studies. The findings of this study can be used in developing new therapeutic modalities as well as new high-tech approaches such as brain-computer interface techniques based on visual interface.<sup>19</sup>

## 5. Conclusion

Our study showed a significant improvement in topographic corneal changes and UDVA results in patients with corneal ectasia after the CXL. These results illustrate the efficacy and usage of CXL for keratoconus among patients with progressive keratoconus. Based on the positive results obtained in various studies conducted

on the efficacy of this method, including the current study, CXL presents an important strategy to halt the progress of keratoconus and improve it, while it can also play an effective role in limiting vision loss.

### Acknowledgments

This article is the result of a research thesis prepared by Masoud Safarzadeh to fulfill the requirements needed for earning the Master of Optometry degree, which was approved by the research committee at IUMS. We appreciate the help of the research center of IUMS. This project is funded by IUMS (94/D/320/3453).

### Abbreviations

|             |   |
|-------------|---|
| $Z\alpha$   | the probability of falsely rejecting a true null hypothesis.  |
| $Z\beta$    | the probability of failing to reject a false null hypothesis. |
| Sd          | Standard deviation.   |
| $\Delta\mu$ | the difference between the value means.                       |

### References

- Rabinowitz YS. Keratoconus. *Surv Ophthalmol.* 1998;42:297–319.
- Kim H, Joo CK. Measure of keratoconus progression using Orbscan II. *J Refract Surg.* 2008;24:600–605.
- Bechrakis N, Blom ML, Stark WJ, Green WR. Recurrent keratoconus. *Cornea.* 1994;13:73–77.
- Pantanelli S, MacRae S, Jeong TM, Yoon G. Characterizing the wave aberration in eyes with keratoconus or penetrating keratoplasty using a high-dynamic range wavefront sensor. *Ophthalmology.* 2007;114:2013–2021.
- Waller SG, Steinert RF, Wagoner MD. Long term results of epikeratoplasty for keratoplasty for keratoconus. *Cornea.* 1995;14:84–88.
- Thompson Jr RW, Price MO, Bowers PJ, Price FW. Long-term graft survival after penetrating keratoplasty. *Ophthalmology.* 2003;110:1396–1402.
- Snibson GR. Collagen cross-linking. A new treatment paradigm in corneal disease: a review. *Clin Experiment Ophthalmol.* 2010;38:141–153.
- Suri K, Hammersmith KM, Nagra PK. Corneal collagen crosslinking: ectasia and beyond. *Curr Opin Ophthalmol.* 2012;23:280–287.
- Ivarsen A, Hjortdal J. Collagen cross-linking for advanced progressive keratoconus. *Cornea.* 2013;32:903–906.
- Wollensak G. Crosslinking treatment of progressive keratoconus; new hope. *Curr Opin Ophthalmol.* 2006;17:357–360.
- Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135:620–627.
- Koller T, Iseli HP, Hafezi F, Vinciguerra P, Seiler T. Scheimpflug imaging of cornea after collagen cross-linking. *Cornea.* 2009;28:510–515.
- Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg.* 2011;37:1282–1290.
- Toprak I, Yildirim C. Effects of corneal collagen cross-linking on corneal topographic indices in patients with keratoconus. *Eye Contact Lens.* 2013;39:385–387.
- Legare ME, Lovieno A, Yeung SN, et al. Corneal collagen cross-linking using riboflavin and ultraviolet A for the treatment of mild to moderate keratoconus: 2 years follow up. *Can J Ophthalmol.* 2013;48:63–68.
- Steinberg J, Ahmadiyar M, Rost A, et al. Anterior and posterior corneal changes after crosslinking for keratoconus. *Optom Vis Sci.* 2014;91:178–186.
- Hashemi H, Seyedian MA, Miraftab M, Fotouhi A, Asgari S. Corneal collagen crosslinking with riboflavin and ultraviolet A irradiation for keratoconus: long-term results. *Ophthalmology.* 2013;120:1515–1520.
- Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia; one year results. *J Cataract Refract Surg.* 2011;37:149–160.
- Ali Y, Abdolhossein B. Brain computer interface: principles, recent advances and clinical challenges. *Orient J Comp Sci Technol.* 2014;7:425–442.